

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 4647PTWO/er	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. PCT/EP2005/051243	International filing date ( <i>day/month/year</i> ) 17 March 2005 (17.03.2005)	Priority date ( <i>day/month/year</i> ) 17 March 2004 (17.03.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SERICHIM S.R.L.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																
2.	<p>This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 15%;"><input checked="" type="checkbox"/> Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/> Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/> Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/> Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/> Box No. I	Basis of the report	<input checked="" type="checkbox"/> Box No. II	Priority	<input type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/> Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/> Box No. VI	Certain documents cited	<input type="checkbox"/> Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/> Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																

	Date of issuance of this report 19 September 2006 (19.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  <b>Agnes Wittmann-Regis</b>
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

REC'D 22 NOV 2005

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To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/EP2005/051243

International filing date (day/month/year)  
17.03.2005

Priority date (day/month/year)  
17.03.2004

International Patent Classification (IPC) or both national classification and IPC  
C07D221/20, C07C231/14

Applicant  
CAFFARO S.r.l.

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2005/051243

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2005/051243

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**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43*bis*.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

- 1) The present application relates to 5-cyano-2,4-dioxo-3-azaspiro[5,5]undecane-1-carboxylic acid (or ester) (VI) useful as intermediate in the preparation of gabapentin precursors and its preparation from cyclohexane with cyanoacetamide followed by further reaction with malonic acid ester.
- 2) Cited documents
  - D1: THOLE F B ET AL: "THE FORMATION AND REACTION OF IMINO-COMPOUNDS. PART XV. THE PRODUCT OF IMINO-DERIVATIVES OF PIPERADINE LEADING TO THE FORMATION OF THE BETABETA-DISUBSTITUTED GLUTARIC ACIDS" JOURNAL OF THE CHEMICAL SOCIETY, TRANSACTIONS, CHEMICAL SOCIETY, LETCHWORTH, GB, no. 99, 1911, pages 422-448, XP001118611 ISSN: 0368-1645
  - D2: ATKINSON ET AL.: "Mechanism of the boron..." J.CHEM.SOC.PERKIN TRANS 1, no. 23, 1976, pages 2457-2462, XP009039957
  - D3: ATKINSON ET AL.: "Synthesis of trispiro..." HELV.CHIM.ACTA, vol. 50, no. 1, 1967, pages 23-43, XP009039956
  - D4: KON ET AL.: "Chemistry of the three..." J.CHEM.SOC.,ABSTRACTS, 1926, pages 2727-2735, XP009039913
  - D5: US-B2-6 613 904 (MONTANARI STEFANIA MARIA PAOLA) 2 September 2003 (2003-09-02)
  - D6: DATABASE REGISTRY [Online] RN 780785-83-3 15 November 2004 (2004-11-15), retrieved from STN

Document D6 indicates an entry date of 15.11.2004, which is after the claimed priority of the present application. On the presumption that the priority is valid for the claimed subject-matter, this document is not considered as prior art.

- 3) Novelty

Document D1 describes the condensation of cyclohexanone with 2 equivalents of cyanoacetamide to result in a product (12 hours) which may subsequently be converted in the diacid III (see in particular page 443). The present intermediate VI is not described.

Documents D2 and D3 describe the analogue reaction of different ketones with

cyanoacetamide and malonate diester (D2, p.2460: 16h.+ 63h; D3, p.29: 14h.+ 24h.).

Document D4 describes the analogue reaction of ketones with malonate diester and ethyl-cyanoacetate; low yields are obtained with the analogue cyclopentan compound whereas a different product resulted for the cyclohexane analogue.

Document D5 refers to the reaction of the prior art presented in scheme 1 of the present application involving the di-cyano compound II (>20 hours).

Accordingly, none of the cited documents D1-D5 discloses the crucial intermediate VI of the present application.

**4) Inventive step**

The present application relates to the problem of providing convenient intermediates in the preparation of gabapentin precursors.

Compared with prior art processes for preparing such precursors, in particular D1 and D6, the presently defined compounds VI are prepared more easily (compare shorter reaction duration) and at the same time allow for effective conversion to gabapentin precursors.

No prior art would suggest such advantages resulting from the preparation route via VI; in this context it is noted that the information on analogue approaches in D2-D4 would actually suggest that such route would not be favourable.

**5) Further observations**

The claims refer to R as including substituted alkyl as well as benzyl. As benzyl would be understood as phenyl substituted C1-alkyl this definition appears inconsistent leaving doubt as to what is meant with substituted alkyl.

In this context it would further appear questionable whether any substituted alkyl for R would actually allow for a solution to the relevant problem, i.e. provision of convenient intermediates for the preparation of gabapentin precursors.